



Prague, Feb 15, 2021

**Review of the Ph.D. dissertation of Rona Karahoda, MSc.**

The doctoral dissertation of Rona Karahoda, MSc., entitled PHYSIOLOGICAL AND PHARMACOLOGICAL ASPECTS OF TRYPTOPHAN AND SEROTONIN HOMEOSTASIS IN THE FETOPLACENTAL UNIT has been submitted at the Faculty of Pharmacy of Charles University, to the doctoral committee of the Pharmacology and Toxicology in 2021. This review has been written for the doctoral committee for the defense of this Ph.D. thesis. Hereby, I declare that I have written the review based on my best expertise and conscience and I do not have any financial or other interest in the result of the procedure.

The thesis has a form of “compact dissertation”, i.e., a compendium of four peer-reviewed papers published in the international journals with impact factor, co-authored by the applicant, plus one paper submitted to an international journal in 2021. It consists of an introduction, an overview of theoretic background and state of the art, followed by the specification of the aims of the dissertation. After the statement of the goals, a brief results section follows, based on short commentaries of the published and submitted papers and clarification of the contributions of the candidate. A summary section, that has a form of general discussion and conclusions follow. The thesis is closed by the list of other published and submitted papers of the candidate, oral and poster contributions related and unrelated to the topic of the thesis, overview of grants awarded to the applicant, and awards and foreign experiences, list of more than 150 cited references, with the original papers prevailing. The thesis is accompanied by four already published papers in very sound journals, namely the International Journal of Biochemistry and Cell Biology, International Journal of Molecular Sciences, Frontiers in Cell and Developmental Biology, and Acta Physiologica. The total impact factor of all published papers is 18.877, which I evaluate as excellent. Most of the journals are in the Q1 of the IF.

In detail, the section on the theoretical background discusses the placental types and development, structure and function of placenta in humans and experimental animals, endocrine and transport functions of the placenta, the role of the placenta in the programming of adulthood diseases and tryptophan metabolism, including serotonin and kynurenine pathways, and effects of antidepressant drugs on the homeostasis of serotonin in the placenta. The aims include investigation of tryptophan flux along the serotonin and kynurenine pathways during gestation in human placenta, elucidation of tryptophan catabolism in the fetoplacental unit during gestation in rat, a comprehensive characterization of serotonin homeostasis in human and rat term placenta, and studies on effects of antidepressant drugs on the serotonin system in the placenta. The results present a trophoblast as a central unit of fetal growth, protection, and programming, roles of various transporters and monoamine oxidase A in uptake and degradation of serotonin by human and rat term placenta, dynamics of tryptophan pathways in humans, and characterization of tryptophan pathways in the fetoplacental unit of the rat in gestation. Overall, the research by Ms. Karahoda provided excellent and valuable results, which underwent rigorous and demanding scrutiny in the scientific journals, resulting in the high quality of the works published in this thesis.

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Regarding the formal side, the thesis is excellent. It is written in very good English and contains all formal prerequisites, such as the table of contents, exhaustive list of abbreviations, and is properly formatted. All abbreviations are explained at the first occurrence in the text. Additionally, the thesis is accompanied by many high-quality images and drawings. All sources of scientific knowledge other than original ones are properly cited. As far as I can judge, the thesis contains all necessary formalities.

I have the following questions for the candidate:

1. What was, in your opinion, the hardest thing that you had to learn during the Ph.D. studies?
2. What is your most important and valuable lesson learned and will you continue in the scientific career after completion of your Ph.D. study?
3. Which of the papers presented in your thesis do you consider the most important one and why?
4. What do you think about the controversial issue of placentophagy in humans, do you think it is of any value?
5. What could be the role of the placenta in the epigenetic transmission of stressful experiences from mother to offspring, can it somehow modify epigenetic stress inheritance?
6. What is known about the metabolism of other biogenic amines in the placenta?

Due to all assets and qualities of the present work, I recommend its evaluation in the council's defense of a Ph.D. degree, and I support awarding Rona Karahoda with a Ph.D. degree, with a high level of enthusiasm.

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